Direct compression of probiotics: A screening study

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INTRODUCTION

Probiotics are promising treatment alternatives for bowel disorders and diseases [1], these intestinal bacteria however are very sensitive towards oxidative degeneration. High compression forces used in order to prepare tablets are known to catalyze the latter [2]. Excipients, so called fillers with binding capacities, offer the possibility to work at lower compaction forces in order to obtain sufficient tablet hardness, low porosity, good disintegration behavior and viable probiotic cells. The filler/binder materials examined in this study are of very different chemical nature and can be co-processed excipients, but should offer good flow ability.

PURPOSE

The aim of this study was to identify a suitable direct compression filler/binder allowing to compact the oxygen sensitive probiotic into immediate release tablets.

EXPERIMENTAL METHODS

After careful blending of 10 % Bifidobacterium longum (freeze-dried powder, Lallemand, France), 1 % magnesium stearate and filler/binder (Nisso HPC SSL, Nisso HPC SSL SFP, Ludiflash, Ludipress, Avicel 302, MicroceLac 100, Startab, Tablettose 80 et Dicalcium phosphate) and optionally 0.7% Aerosil 200 (for Hydroxypropyl cellulose only) directly compressed tablets were prepared with a fully instrumented benchtop tablet press (StylOne Nano, Medelpharm), equipped with flat-faced punches (diameter: 11.28 mm) at a compression speed of 10 mm/s and a fill shoe agitation of 10 to 20 Hz. The mass of the tablets was kept constant at 500 mg. According to the Ph.Eur. the tablet hardness (Schleuniger 5Y tablet tester) as well as the disintegration time of tablets with hardnesses of around 100 N was analyzed in demineralized water. The true density (δ_{true}) and funnel flow behavior of the pure excipient or optionally under addition of the flow-aid Aerosil 200 (0.7%, with hydroxypropyl cellulose only) was analyzed according to the Pharmacopeia (n=3). The compaction behavior of the powder blends was investigated by adjusting the lower punch displacement to obtain different compression forces. Particle sizes were measured with the laser diffraction method (Mastersizer S, Malvern Panalytical) in air dispersion, the results are expressed as the diameter of the particles of the different volume fractions (0.5, 0.1 & 0.9).

RESULTS AND DISCUSSION

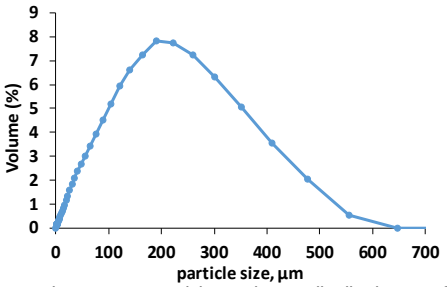

Fig. 1: Particle size distribution of Bifidobacterium longum powder used within this study (δ_{true}: 1.369 g/cm³, $d_{V0.5}$: 132.9 µm).

Brand name	Chemical nature	Particle size: $d_{V0.5}$, $d_{V0.1}$ & $d_{V0.9}$ (µm)	δ_{true} (g/cm³)	Funnel flow time (s)
Nisso HPC® SSL	Hydroxypropyl cellulose	57.9 11.9, 158.6	1.232 ±0.005	26.1 ±4.1
Nisso HPC® SSL SFP	Hydroxypropyl cellulose	17.8 4.9, 35.5	1.165 ±0.002	82.3 ±9.9
Excipress® SD2	Lactose monohydrate	55.4 16.9, 137.7	1.584 ±0.002	4.8 ±0.8
SuperTab® 24AN	Lactose anhydrous	85.1 19.6, 200.5	1.546 ±0.003	5.3 ±0.1
Dicalcium phosphate	Dicalcium phosphate	175.0 83.6, 277.7	2.355 ±0.002	6.9 ±0.6
Avicel® 302	Microcrystalline cellulose (MCC)	118.4 27.6, 254.0	1.513 ±0.003	16.8 ±4.0
StarTab®	Starch	81.6 25.4, 169.2	1.514 ±0.003	4.0 ±0.1
Ludiflash®	Co-processed mannitol, crospovidone, polyvinylacetate & povidone	64.8 12.8, 221,3	1.411 ±0.001	4.5 ±0.2
Ludipress®	Co-processed lactose, crospovidone & povidone	174.3 52.8, 327.3	1.523 ±0.000	6.1 ±0.7
MicroceLac® 100	Co-processed Lactose and MCC	135.7 36.4, 261.8	1.556 ±0.010	6.3 ±0.4

Table 1: Properties of filler/binder excipients used within this study.

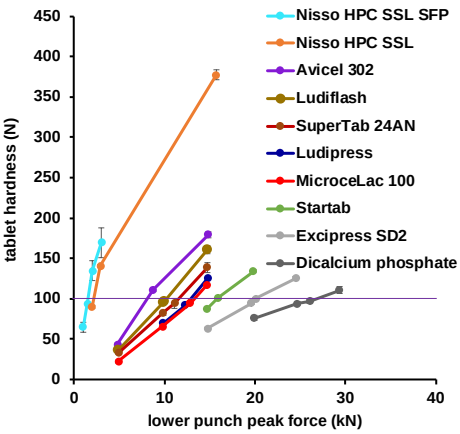

Fig. 2: Manufacturability diagrams of powder blends based on various filler/binder candidates into tablets (n=5).

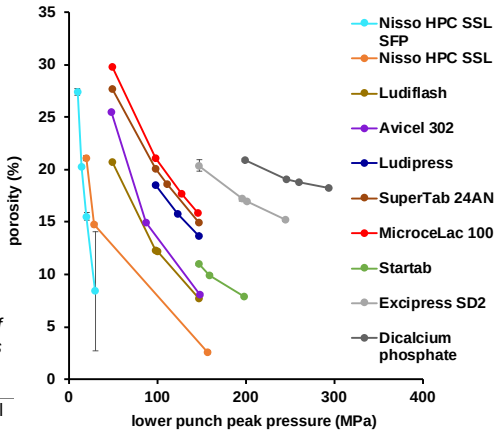

Fig. 3: Compactibility of powder blends: In-die porosity as a function of the lower punch peak pressure (n=5).

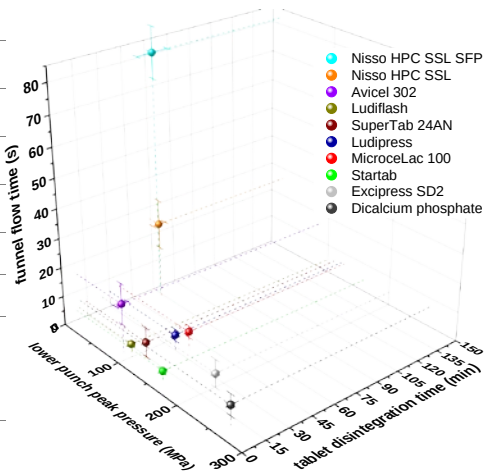

Fig. 4: Scatter plot taking into consideration the flow ability of the excipient, the compaction force necessary to produce tablets with a hardness of 100 N and the disintegration time of the latter.

CONCLUSIONS

The filler/binder excipients employed within this study offer very different advantages. Especially designed to allow excellent flow ability, several of them still demand high compaction forces to result into tablets with suitable hardness to allow for probiotic viability. Hydroxypropyl cellulose based products offer good compactibility at low compression pressures, but show very poor flow ability and disintegration times of tablets. In this present case the most promising filler/binder candidates, combining low funnel flow times, high manufacturability and fast tablet disintegration, were identified to be, Ludiflash and alternatively Avicel 302.

REFERENCES

[1] Kumar, M. et al. Int J Probiotics & Prebiotics 11, 99-116, 2016.

[2] Allouche, R. et al. Int J Pharm 538, 14-20, 2018.